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Practical Synthesis of Chiral Vinylphosphine Oxides by Direct Nucleophilic Substitution. Stereodivergent Synthesis of Aminophosphine Ligands

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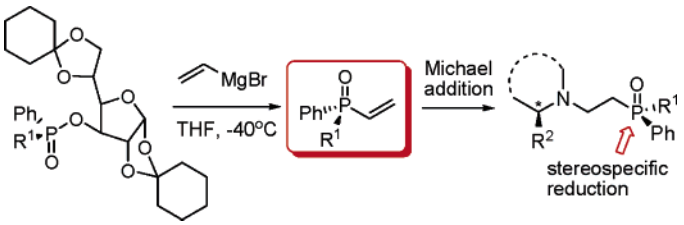

A practical synthesis of optically pure alkylphenylvinylphosphine oxides is described, utilizing a nucleophilic displacement at phosphorus to install the vinyl moiety. The products were used to prepare classes of P-stereogenic aminophosphine (PN) and aminohydroxyphosphine (PNO) ligands. Stereocontrol can be exerted at various stages of the synthesis, to provide specific combinations of chirality in the final product. The effect of the stereogenic phosphorus and match−mismatch of chiralities of PNO ligands were examined in the asymmetric ruthenium-catalyzed hydrogen transfer reduction of three aryl ketones.

Introduction

P-Stereogenic vinylphosphine oxides can be transformed by a variety of reactions to give structures of considerable structural complexity, making them highly valuable as precursors for the synthesis of phosphorus ligands for asymmetric catalysis.[1] Discounting chiral resolution by preparative HPLC methods,[2] which are impractical on a large scale, there is a general lack of synthetic procedures for homochiral vinylphosphine oxides. Typically, they are prepared via chiral phosphinate ester intermediates[3] that were resolved either enzymatically or by the formation of diastereomeric menthyl esters.[1j,4] Because of its inherent reactivity, the double bond is often installed by elimination reactions in the last stages of the synthesis. To date, asymmetric synthesis of vinylphosphine oxides via the direct nucleophilic substitution of a O=PXYZ compound by H_2C=CHMgX has never been successful,[5] although reactions with other Grignard reagents are known to proceed in a highly stereospecific manner.[6] This is because the conjugate addition of the organometallic reagent to the vinylphosphine oxide

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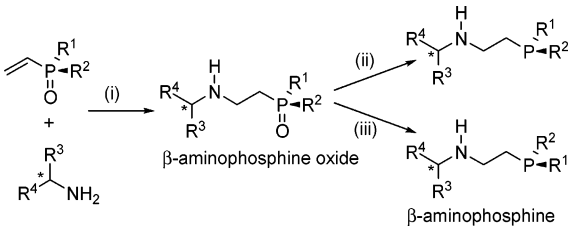
SCHEME 1. Stereodivergent Synthesis of *β*-Aminophosphine Ligands[a]



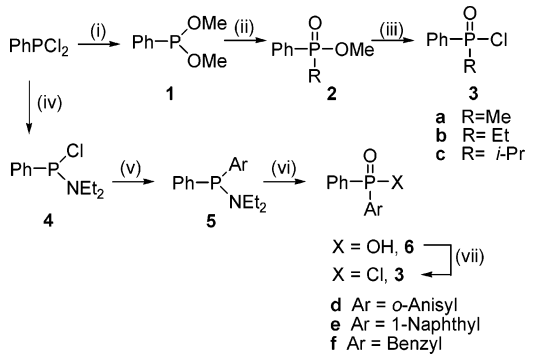
[a] (i) Michael addition; (ii) reduction with retention of configuration; (iii) reduction with inversion of configuration.

product is competitive under the reaction conditions required for the nucleophilic substitution.[7]

As part of our research directed toward the catalytic applications of bidentate (PN) and terdentate (PNP, PNN, PNO) aminophosphine ligands, we have developed a number of methodologies for the synthesis of ligands containing stereogenic carbon and phosphorus atoms.[8,9] During the course of this work, we became particularly interested in utilizing aza-Michael addition as a means of accessing chiral *β*-aminophosphines containing chirality at the N- and P-termini. By judicious selection of the appropriate isomers of amine and vinylphosphine oxide precursors, different structures and chirality can be assembled in a single step. Furthermore, by choosing the appropriate reagents, the reduction of phosphine oxide can be achieved stereospecifically with either retention or inversion of configuration, delivering great stereodiversity to the process (Scheme 1).

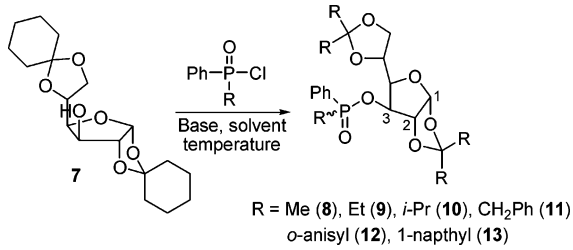
In our quest to develop a general route to the synthesis of optically pure vinylphosphine oxide precursors, we were attracted by a report by Khiar and Fernández et al., who described the stereoselective synthesis of tertiary *o*-anisyl and *n*-propyl methylphenylphosphine oxides by nucleophilic displacement of phosphinate esters prepared from sugar derivatives.[10] The reactions with alkyl and aryl Grignard reagents were reported to occur under very mild conditions (room temperature, 2 h), but the reaction with vinyl Grignard reagents was not reported. Herein, we will describe how this method can be modified to achieve stereoselective, gram-scale synthesis of optically active vinylphosphine oxides, which can be used in the synthesis of a number of P-stereogenic PN and PNO ligands, containing one or more stereogenic centers. Finally, some results obtained from the application of these ligands in the asymmetric transfer hydrogenation reactions will be discussed.

SCHEME 2. Synthesis of (±)-Alkylphenyl and Arylphenylphosphinic Chlorides[a]



[a] (i) MeOH, pyridine, hexane, 0 °C; (ii) RI, reflux (R = alkyl); (iii) PCl_5, CH_2Cl_2, reflux; (iv) $HNEt_2$, pyridine, THF, reflux, 3 h; (v) ArMgBr, THF, 0°C; (vi) H_2O_2, concentrated HCl, acetone; (vii) $SOCl_2$.

SCHEME 3. Formation of Phosphinate Esters



Result and Discussion

Preparation of Phosphinic Chlorides. Asymmetric phosphinic chlorides were prepared using established literature procedures.[6] For alkylphenylphosphinic chlorides, dichlorophenylphosphine was subjected to alcoholysis to give dialkyl phosphonites **1**. Michaelis−Arbusov reaction with the relevant alkyl halides gave the phosphinate esters **2**, which were chlorinated to afford the phosphinic chorides **3a**−**c** (Scheme 2). On the other hand, aryl- and benzylphenylphosphinoyl chlorides **3d**−**f** were prepared by the chemoselective substitution of chlorophenylphosphoramide **4**, using the requisite aryl Grignard reagents.[11] The resulting arylphenylphosphonamides **5d**−**f** were promptly oxidized and hydrolyzed in one pot, to yield asymmetric arylphenylphosphinic acids **6d**−**f**. Subsequent chlorination afforded the arylphenylphosphinic chlorides **3d**−**f**.

Formation of Phosphinate Esters (Scheme 3, Table 1). In the absence of detailed experimental procedures, the reaction between 1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (DCG), **7**, and methylphenylphosphinic chloride **3a** was reexamined. The initial reaction was conducted in toluene at 0 °C, employing triethylamine as the base and an excess of the methylphenylphosphinic chloride **3a** (10 equiv). The progress of the reaction was monitored by TLC analysis and quenched upon complete consumption of the chiral auxiliary. Following workup and column chromatography, the corresponding phosphinate ester

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TABLE 1. Reaction of Methylphenylphosphinic Chloride 3a with DCG[a,b]

entry	equiv[c]	base	solvent	*t*/h	*T*/°C	d.r.[d]
1	10	Et_3N	toluene	8	0	95:5
2	3	Et_3N	toluene	18	0	95:5
3	1	Et_3N	toluene	24	0	95:5
4	1	Et_3N	toluene	48	−78	95:5
5	1	Et_3N	toluene	15	25	92:8
6	1	Et_3N	THF	24	0	87:13
7	1	Et_3N	CH_2Cl_2	24	0	80:20
8	1	Pyr	toluene	24	0	40:60
9	1	Pyr	THF	24	0	30:70

[a] Scheme 3, R = Me. [b] All reactions were performed using 1 equiv of **7** and 3 equiv of the appropriate base. [c] Equivalents of methylphenylphosphinic chloride **3a**. [d] S_P/R_P epimeric ratio, determined by ^{1}H NMR analysis.

TABLE 2. Reaction of Racemic Phenylphosphinic Chlorides 3b−f with 7[a,b]

entry	substrate	R	product	base	solvent	yield (%)[c]	d.r.[d]
1	**3b**	Et	**9**	Et_3N	toluene	93	93:7
2	**3b**	Et	**9**	Pyr	THF	94	30:70
3	**3c**	*i*-Pr	**10**	Et_3N	toluene	92	86:14
4	**3c**	*i*-Pr	**10**	Pyr	THF	90	40:60
5	**3f**	Bn	**11**	Et_3N	toluene	95	90:10
6	**3f**	Bn	**11**	Pyr	THF	95	40:60
7	**3d**	*o*-anisyl	**12**	Et_3N	toluene	93	30:70
8	**3d**	*o*-anisyl	**12**	Pyr	THF	94	55:45
9	**3e**	1-naphthyl	**13**	Et_3N	toluene	87	40:60
10	**3e**	1-naphthyl	**13**	Pyr	THF	83	55:45

[a] Scheme 3. [b] The reactions were performed at 0 °C using **3b−f** (10 mmol), **7** (1.5 equiv), and the appropriate base (3 equiv). [c] Isolated yield after column chromatography. [d] Determined by ^{1}H NMR analysis.

8 can be obtained in near quantitative yields. The diastereomeric ratio can be determined by ^{1}H NMR analysis, by comparing resonances of H-1, H-2, and H-3 corresponding to each epimer, which are separated by large anisotropic shifts.[12] Alternatively, the diastereomeric excess (de) of **8** can also be determined by HPLC analysis.[13] The product was found to have a de of 90% (Table 1, entry 1).

Contrary to a previous report,[10b] the diastereomeric ratio remained unchanged when the reactants were used in equimolar amounts, even at lower temperature (entries 2−4). At room temperature, the reaction experienced a slight erosion of de (entry 5). The reaction was noticeably slower in more polar solvents (dichloromethane, THF), which also led to a reduction in the selectivity (entries 6 and 7). The effect of the achiral base had been identified as the most important factor that determines the stereochemical outcome of the reaction.[9b,c] Indeed, the selectivity was reversed in the presence of pyridine (entries 8 and 9).

Subsequently, reactions of phosphinic chlorides **3b−g** with **7** were performed using the two bases at 0 °C (Table 2). As these reactions are slower, a slight excess of the DCG (1.5 equiv) was employed.[14] The phosphinate esters **9−13** were obtained with good to excellent yields after column chromatography, which also permitted the recovery of the excess chiral auxiliary.

Once again, the stereochemical outcome of the reactions was directly dependent on the nature of the achiral base used in the reaction (Table 2). In the presence of triethylamine, the ethyl and benzyl phosphinate esters **9** and **11** were obtained with high diastereomeric excesses (entries 1 and 5).[15] An increase in the size of the alkyl group resulted in a decrease in stereodifferentiation, as shown by the lower de obtained with the isopropyl derivative **10** (entry 3).

The diastereomers of phosphinate esters **8−11** were separated easily on a large scale; up to 5 g can be separated effectively on a preparative (flash) column to afford optically pure isomers (de > 99%, determined by HPLC).

It would appear that DCG is not a good selector for asymmetrical diarylphosphine oxides. By replacing the alkyl substituent on phosphorus with an aryl group, a significant drop in stereoselectivity was observed (Table 2, entries 7−9). As a result, the separation of the diastereomers proved to be problematic. Despite several repeated chromatographic runs using a variety of eluting systems and stationary phases, the *o*-anisyl-substituted phosphinate ester **12** can only be obtained in an optically enriched form (de ≤ 95%), whereas the epimeric separation of **13** remained elusive.

TABLE 3. Chemical Shifts, Optical Rotation, and Configurational Assignments for 8−12

	^{1}H NMR chemical shift (ppm)[a]				
compound	H-1	H-2	H-3	$[\alpha]_D$[b]	assignment
8	5.90	5.04	4.37	−58.6	S_P[c]
	5.79	4.64	4.87	−31.5	R_P[c]
9	5.89	5.07	4.44	−54.2	S_P
	5.75	4.58	4.90	−27.1	R_P
10	5.96	5.20	4.55	−51.0	S_P
	5.72	4.52	4.96	−12.3	R_P
11	5.75	4.84	4.45	−53.4	S_P
	5.80	4.59	4.81	−17.0	R_P
12	5.87	5.10	4.70	−39.0[d]	R_P
	5.83	4.94	4.72	−9.0[e]	S_P

[a] Unless otherwise stated, ^{1}H NMR (360 MHz, $CDCl_3$) spectra were recorded with optically pure samples (de > 99%, verified by HPLC analysis). [b] Optical rotations were measured in $CHCl_3$. [c] Reported absolute configuration.[10b] [d] de = 92%. [e] de = 95%.

Key spectroscopic and optical properties of the phosphinate esters **8−12** are presented in Table 3. The absolute configuration of the major epimer of compound **8** obtained using triethylamine (S_P) has been previously established.[10b] Notably, it displayed a distinctive distribution of proton resonances, whereby the H-3 signal (double-doublet) is shifted *upfield* with respect to H-2. This is reversed for the opposite epimer (R_P)-**8**, where the H-3 resonance is located *downfield* to H-2. This trend appears to be consistent for all the alkylphenylphosphinate esters (see Supporting Information). Thus, the absolute configurations of **9−11** were tentatively assigned by this analogy. These were confirmed

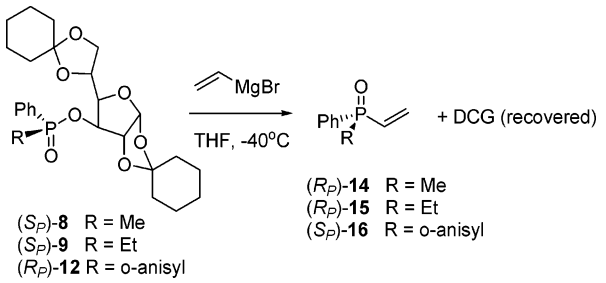
(12) Resonances attributed to protons H-1 and H-2 appeared as distinct doublets in the region 6.00−4.50 ppm. For the S_P diastereoisomer, the H-3 resonance is shifted upfield to H-2, whereas the opposite is true for the R_P isomer (Supporting Information).

(13) HPLC conditions: Hicrom Partisil P5 Silicon column, 95:5 hexane/*i*-PrOH, flow rate of 1 mL/min, t_R = 7.41 min, and t_S = 9.23 min.

(14) The reaction progress was monitored by ^{31}P-{^{1}H} NMR analysis. Aliquots of the reaction mixture were extracted periodically and quenched immediately by the addition of water. Reaction was terminated upon complete consumption of the starting phosphinic chloride (acid). The formation of epimers was indicated by the appearance of two resonance signals.

(15) The origin(s) of the base-directed stereoselectivity is not clear at this juncture. However, the unchanged de at different reactant ratios (Table 1, entries 1−3) suggests that the process is unlikely to be the result of a dynamic kinetic resolution, which would be expected to be concentration dependent. The Et_3N/toluene (strong base/nonpolar solvent) system could generate a nucleophilic alkoxide with a different selectivity to the alcohol, and/or, conversely, the use of pyridine/THF could alter the nature of the electrophile; e.g., the nucleophilic pyridine can attach itself to the phosphorus center, generating a phosphonium intermediate (stabilized by the polar solvent).

SCHEME 4. Nucleophilic Displacement of DCG by Vinylmagnesium Bromide



later by chemical conversion of **8** and **9** into phosphine oxides of known configuration. Although such correlations were not achieved for **10** and **11**, it is not unreasonable to assume that the NMR assignment is consistent.

For the arylphosphinate ester **12**, the H-3 resonance signal appeared upfield to H-2 for both epimers. For these isomers, stereochemical assignments were made by chemical correlation (vide infra).

Thus, in a predictable manner, the use of triethylamine in the reaction between alkylphenylphosphinic chloride and **7** led predominantly to the formation of the (S_P)-phosphinate ester, whereas pyridine promoted the formation of the opposite epimer. When arylphenylphosphinic chlorides are employed, the (R_P)-phosphinate was obtained as the major product with triethylamine and the (S_P)-phosphinate was slightly preferred with pyridine.[16]

Displacement of the Chiral Auxiliary: Synthesis of Enantiopure Vinylphosphine Oxides (Scheme 4). In the original reports, nucleophilic displacements of the DCG by Grignard reagents were effected at room temperature. To suppress the Michael addition, we conducted the reaction at much lower reaction temperatures. After some trial and error, the optimal temperature was found to be −40 °C, whereupon the reaction of (S_P)-**8** with vinylmagnesium bromide proceeded smoothly to give methylphenylvinylphosphine oxide **14**.

The reaction is extremely sensitive to the reaction temperature. Crucially, the Grignard reagent (3 equiv) has to be added slowly at −78 °C, before the temperature is raised to −40 °C, where it is maintained until all the phosphinate ester is consumed (^{31}P NMR).[17] It is also important to quench the reaction at 0 °C. Using this procedure, one can isolate methylphenylvinylphosphine oxide **14** in 80% yield after purification by column chromatography. The product was found to have the R_P configuration, by comparison of its optical rotation, $[\alpha]_D$ = +81.7°, which was opposite in sign to the reported value of the S_P isomer ($[\alpha]_D$ = −80°).[18] Hence, the nucleophilic substitution had occurred with inversion of configuration at phosphorus. Similarly, ethylphenylvinylphosphine oxide (R_P)-**15** may be obtained from phosphinate (S_P)-**9** in 72% yield ($[\alpha]_D$ = +77.5°). The opposite enantiomers (S_P)-**14** and -**15** were also obtained from (R_P)-**8** and -**9** in good yields.

Slow crystallization from ether at −5 °C afforded single crystals of (R_P)-**14** and -**15** in sufficiently good quality to enable the absolute configurations to be determined unequivocally

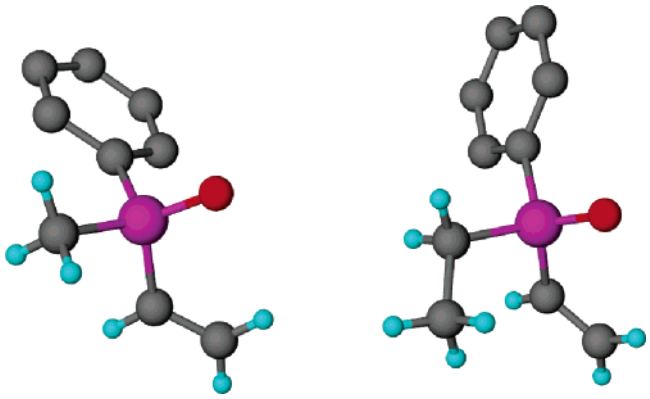


FIGURE 1. Molecular structures of alkylvinylphenylphosphine oxides **14** (left) and **15** (right) showing the requisite R_P stereochemistry (aromatic hydrogens are omitted to aid clarity).

(Figure 1).[19] Also, although there are four different molecules of **14** in the asymmetric unit, they only differ by the rotation of the phenyl ring (Supporting Information).

A good result was also obtained for the displacement of the optically enriched **12** (92% de), which furnished the *o*-anisylphenylvinylphosphine oxide **16** in 75% isolated yield. At this point, its configuration (R_P) can be established by comparison of its optical rotation, $[\alpha]_D$ = +7.9°, with the reported value ($[\alpha]_D$ = +8.8°).[1j] The value is consistent with an optical purity of 92% (0.92 × 8.8°), which confirms the stereospecificity of the substitution reaction. Assuming that this has also proceeded with inversion of configuration at phosphorus, it follows that the phosphinate ester **12** has the R_P configuration.

The nucleophilic substitution reactions proved to be sensitive to the alkyl group at phosphorus. No reaction between the isopropyl derivative **10** and vinylmagnesium bromide could be detected (^{31}P NMR), even when a large excess of Grignard reagent (10 equiv) was employed. Presumably, the nucleophilic substitution is prevented by insurmountable steric congestion at phosphorus. Conversely, the addition of the vinyl Grignard reagent to the benzyl phosphinate ester **11** also failed to give the desired vinylphosphine oxide. Even though a bright red reaction mixture was obtained, only the starting material was recovered upon workup. We attributed this failure to the acidity of the benzylic protons, which could be deprotonated by the organometallic reagent. Because the Michael addition can be suppressed under these reaction conditions, we envisage that these problems may be circumvented by introducing the vinyl moiety at an earlier stage, i.e., adding the benzyl or isopropyl Grignard reagent to a diastereomerically pure sample of vinylphenylphosphinate ester. Because a variety of vinylphosphine oxides may be accessible through one common phosphinate ester, it is also a more attractive strategy; this will be explored in our future work.

Synthesis of Homochiral *β*-Aminophosphines by the Aza-Michael Addition. The conjugate addition of amines should proceed without loss of stereointegrity at the phosphorus atom. Previously, Pietrusiewicz et al. demonstrated that the Michael addition of amines to P-stereogenic vinylphosphine oxides

(16) Note that substitution of alkyl by aryl in these phenylphosphinate esters neccesitates a change in the chiral descriptor; the stereoinduction of the achiral base is unchanged for all the substrates.

(17) Side-product formation was observed at −20 °C.

(18) Pietrusiewicz, K. M.; Zablocka, M.; Monkiewicz, J. *J. Org. Chem.* **1984**, *49*, 1522.

(19) Absolute structure parameters for **14** = 0.06(7) and **15** = −0.06(9). Although the esds for the latter structure is slightly higher, the absolute configuration of this molecule has been corroborated by comparison of its $[\alpha]_D$ with the reported value. The X-ray crystal structure of (*S*)-**14** was previously reported: Pietrusiewicz, K. M.; Zablocka, M.; Wieczorek, W.; Brandi, A. *Tetrahedron: Asymmetry* **1991**, *2*, 419.

occurs slowly in water (7 days heating in a sealed ampule).[20] We have subsequently found that the addition can be dramatically accelerated in the presence of methanol. In all cases, reaction was complete in just a few hours, even with the most sterically demanding *tert*-butylamine.[8f] We have used the methodology to assemble aminophosphine and aminophosphine oxide ligands from commercially available chiral amines and amino alcohols.[9c]

Thus, both isomers of methylphenylvinylphosphine oxide **14** were subjected to Michael addition reactions with a number of achiral, as well as optically active, amines and amino alcohols. Reactions were complete in a few hours (^{31}P NMR), to afford P-chiral phosphine oxides **17**−**24** in near quantitative yields after purification via column chromatography (Table 4). Single sets of ^{1}H and ^{31}P NMR resonances were observed for the addition of homochiral amines; thus, the optical purity of the products were judged to be at least >95%.

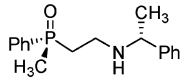
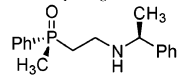
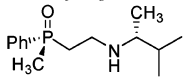
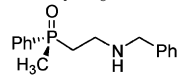
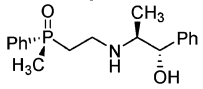
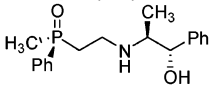
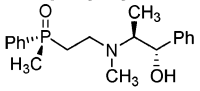
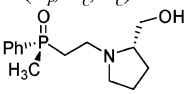
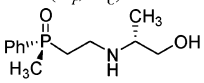
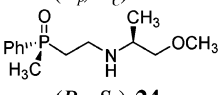
The aminophosphine oxides **17**, **19**, and **20** were reduced stereoselectively with inversion of configuration, using $HSiCl_3$ and triethylamine,[21] to the corresponding new P-stereogenic phosphines **25**−**27** (Figure 2) in good yields (70−80%). The optical rotary values of **25** corresponded well with those reported for their enantiomers.[20b] Again, no loss of the optical purity was observed. This was confirmed by subjecting (R_P)-**26** to oxidation by H_2O_2 in $CHCl_3$, which is known to occur with retention of configuration.[22] This provided (S_P)-**19**, which exhibited specific optical rotation equal in magnitude but opposite in sign to its enantiomer (Table 4, entry 4). This experiment also illustrates the versatility of the methodology, which may be manipulated to obtain the required P-chirality in the ligand, by choosing the appropriate reduction/oxidation reagents. Thus, the stereochemistry can be defined in the final transformation step, allowing simple access to P-chirality without recourse to unnatural L-glucose.

Catalytic Studies (Scheme 5, Table 5). Previously, we have found that hydroxyaminophosphine ligands derived from chiral amino alcohols confer extremely catalytic activity and selectivity in ruthenium-catalyzed asymmetric transfer hydrogenation reactions.[9b,c] Herein, we disclose some preliminary catalytic studies carried out using the P-stereogenic hydroxyaminophosphine ligands derived from (R_P)-**14**. The results will be compared with those obtained with the diphenylphosphines **29**−**31** prepared earlier (Figure 3).[9c]

Using the reaction conditions previously optimized for P−N−O ligands, the asymmetric transfer hydrogenation reactions of three aryl ketones (acetophenone, propiophenone, and 1-phenylbutan-1-one) were carried out at room temperature using 2-propanol as the hydrogen source.

Previously, we have established that hydroxyaminophosphine oxide (PNO) ligands derived from ephedrine are noticeably more stereoselective than PN ligands generated from other amines. Furthermore, chirality at phosphorus has a small but significant effect on the enantioselectivity. These observations are reinforced in the present study: Ligands **20** afforded much higher conversion and enantioselectivity than the corresponding ligand derived from L-alaninol (entries 1−3 vs 7−9, entries 4−6 vs 10−12). The ligand (S_P,R_C,S_C)-**20** is particularly selective, conferring enantiomeric excesses (ee's) in excess of 90% for the reduction of all three ketones. In the absence of the stereogenic phosphorus, the ligand (R_C,S_C)-**28** afforded products

TABLE 4. Yields and Optical Rotations of Chiral Aminophosphines and Aminohydroxyphosphines[a]

Entry	Product	$[\alpha]_D$ [b]	Yield (%)[c]
1	 (R_P, R_C)-**17**	-25.5° (c = 2.7)[d]	97
2	 (R_P, S_C)-**17**	+50.7° (c = 2.8)[e]	98
3	 (R_P, R_C)-**18**	+10.6° (c = 1.0)	98
4	 (R_P)-**19**	+17.7° (c = 2.0)	98
5	 (R_P, R_C, S_C)-**20**	+27.7° (c = 3.1)	95
6	 (S_P, R_C, S_C)-**20**	-31.2° (c = 1.0)	94
7	 (R_P, R_C, S_C)-**21**	+8.2° (c = 1.2)	87
8	 (R_P, R_C)-**22**	-15.2° (c = 1.2)	92
9	 (R_P, R_C)-**23**	+1.5° (c = 1.1)	94
10	 (R_P, S_C)-**24**	+29.5° (c = 1.0)	93

[a] Diastereomeric purity >95%, determined by ^{1}H NMR analysis. [b] Recorded in $CHCl_3$. [c] Isolated yields. [d] Reported $[\alpha]_D$ of the S_P, S_C enantiomer[20b] = +27.3 ($CHCl_3$, c = 5.3). [e] Reported $[\alpha]_D$ of the S_P, R_C enantiomer[20b] = −56.1 ($CHCl_3$, c = 3.2).

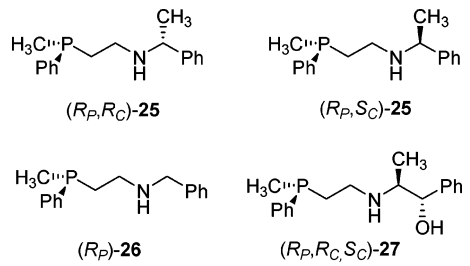


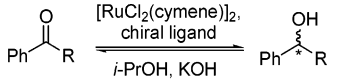
FIGURE 2. P-Stereogenic β-aminophosphines and aminohydroxyphosphines.

(20) (a) Maj, A. M.; Pietrusiewicz, K. M.; Suisse, I.; Agbosou, F.; Mortreux, A. *Tetrahedron: Asymmetry* **1999**, *10*, 831. (b) Maj, A. M.; Pietrusiewicz, K. M.; Suisse, I.; Agbosou, F.; Mortreux, A. *J. Organomet. Chem.* **2001**, *626*, 157.

(21) (a) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc*. **1969**, *91*, 7012. (b) Horner, L.; Balzer, W. D. *Tetrahedron Lett*. **1965**, *6*, 1157.

(22) Horner, L. *Pure Appl. Chem*. **1964**, *9*, 225.

SCHEME 5. Asymmetric Ruthenium-Catalyzed Transfer Hydrogenation of Aryl Ketones



with ee's around 90% (entries 7−9). In the presence of a (R_P)-phosphine oxide moiety, ligand **20** improved the yields of the alcohols by up to 10%. However, although the enantioselectivity remained unchanged for the reduction of acetophenone, optical purities of the other products were noticeably reduced (entries 10−12). By changing the chirality at phosphorus to (S_P)-**20**, the ee's of the products were significantly enhanced (entries 13−15), and the catalytic activities were maintained. Hence, there are clear cooperative effects between the stereogenic centers on the enantioselectivity but not on the catalytic activity of the process. The stereoinduction is unaffected by the stereochemistry at phosphorus.

Reduction of the phosphorus moiety to the +3 oxidation state reduced the catalytic activity of the resultant catalysts (entries 16−21). Once again, P-chirality was found to have an effect on the enantioselectivity of the processes, but it is not significant enough to change the overall stereoinduction.

Conclusion

A practical synthesis of optically pure alkylphenylvinylphosphine oxides has been achieved in five steps from dichlorophenylphosphine, involving the nucleophilic displacement of a DCG derivative by a vinyl Grignard reagent at low temperature. The methodology proved to be well suited for large-scale preparation of these valuable precursors. Utilizing the Michael reaction, one can prepare a variety of optically pure aminophosphine ligands, and stereochemistry of the ligands can be controlled in a predictable manner. Finally, cooperative effects between donor atoms, chirality, and oxidation state of the phosphorus moiety are demonstrated in the ruthenium-catalyzed asymmetric transfer hydrogenation reactions of ketones.

Experimental Section

Synthesis and Resolution of Dicyclohexylidene-D-glucose Phosphinate Esters. Et_3N (3 equiv) was added to an ice-cold solution of the appropriate phosphinic chloride (10 mmol) in toluene (25 mL) and stirred for 10 min. A solution of di-*o*-cyclohexylidene-α-D-glucofuranose (1.2 equiv) in toluene (25 mL) was then added slowly over 30 min. The reaction mixture was allowed to warm to room temperature, and stirring was continued until all the phosphinic chloride was consumed (^{31}P NMR). The mixture was filtered, and the solvent was removed under reduced pressure. The crude product was purified by passing through a short silica column, eluting with ether, to recover any unreacted alcohol (DCG). Diastereomeric separation was achieved chromatographically on flash silica gel using a mixture of ether/acetone (9:1). Diastereomeric excess (de) was determined either by normal-phase HPLC (silicon column, flow rate of 1.0 mL/min, 95:5 hexane/*i*-PrOH) or by reverse-phase HPLC (C18 column, flow rate of 0.5 mL/min, MeOH/H_2O, gradient 60:40, 30 min; 95:5, 40 min; and 60:40, 30 min).

Dicyclohexylidene-D-glucose-(S_P)-methylphenyl Phosphinate Ester, (S_P)-8. White solid, 98%, mp 49−51 °C. $[\alpha]^{20}_D$ −58.6° (*c* 1.0, $CHCl_3$). δ_H (360 MHz, $CDCl_3$): 1.20−1.66 (20H, m, CH_2), 1.65 (3H, d, J_{HP} = 14.5, PCH_3), 3.92−3.98 (2H, m, H_4, H_6), 4.08 (1H, dd, J_{HH} = 8.6, 5.9, H_6), 4.23 (1H, ddd, J_{HH} = 8.6, 5.4, 4.5, H_5), 4.37 (1H, dd, J_{HP} = 6.8, J_{HH} = 2.3, H_3), 5.04 (1H, d, J_{HH} = 3.6, H_2), 5.90 (1H, d, J_{HH} = 3.6, H_1), 7.84−7.91 (2H, m, H_{meta}), 7.49−7.55 (1H, m, H_{para}), 7.84−7.91 (2H, m, H_{ortho}). δ_C (90.6 MHz, $CDCl_3$): 16.0 (d, J_{CP} = 105, PCH_3), 23.9 (s, CH_2), 24.1 (s, CH_2), 24.6 (s, CH_2), 24.8 (s, CH_2), 25.2 (s, CH_2), 25.5 (s, CH_2), 35.3 (s, CH_2), 36.1 (s, CH_2), 37.0 (s, CH_2), 67.5 (s, C_6), 72.0 (s, C_5), 78.5 (d, J_{CP} = 7, C_3), 81.1 (d, J_{CP} = 9, C_4), 83.7 (s, C_2), 105.1 (s, C_1), 110.4 (s, *C*), 113.1 (s, *C*), 129.8 (d, J_{CP} = 13, C_{meta}), 136.6 (d, J_{CP} = 11, C_{ortho}), 132.8 (d, J_{CP} = 134, C_{ipso}), 133.1 (d, J_{CP} = 3, C_{para}). δ_P (145.8 MHz, $CDCl_3$): +46.4. ν_{max} (KBr disk)/cm^{-1}: 1173 (s, P═O). HRMS (EI) *m*/*z*: 501.2032 (M + Na^+). Calcd for $C_{25}H_{35}NaO_7P$: 501.2018.

Dicyclohexylidene-D-glucose-(R_P)-methylphenyl Phosphinate Ester, (R_P)-8. White solid, 98%, mp 49−50 °C. $[\alpha]^{20}_D$ −31.5° (*c* 1.0, $CHCl_3$). δ_H (360 MHz, $CDCl_3$): 1.20−1.66 (20H, m, CH_2), 1.73 (3H, d, J_{HP} = 14.5, PCH_3), 3.96 (1H, dd, J_{HH} = 8.6, 4.5, H_6), 4.07−4.14 (2H, m, H_6, H_4), 4.21 (1H, ddd, J_{HH} = 8.6, 5.4, 4.5, H_5), 4.64 (1H, d, J_{HH} = 3.6, H_2), 4.87 (1H, dd, J_{HP} = 9.1, J_{HH} = 2.7, H_3), 5.79 (1H, d, J_{HH} = 3.6, H_1), 7.39−7.46 (2H, m, H_{meta}), 7.48−7.54 (1H, m, H_{para}), 7.70−7.78 (2H, m, H_{ortho}). δ_C (90.6 MHz, $CDCl_3$): 15.5 (d, J_{CP} = 95, PCH_3), 23.8 (s, CH_2), 24.2 (s, CH_2), 24.3 (s, CH_2), 24.5 (CH_2), 25.2 (s, CH_2), 25.5 (s, CH_2), 36.0 (s, CH_2), 36.8 (s, CH_2), 37.0 (s, CH_2), 67.7 (s, C_6), 72.6 (s, C_5), 77.9 (d, J_{CP} = 7, C_3), 81.4 (d, J_{CP} = 7, C_4), 84.0 (s, C_2), 105.3 (s, C_1), 110.4 (s, *C*), 113.5 (s, *C*), 129.0 (d, J_{CP} = 13, C_{meta}), 130.0 (d, J_{HP} = 11, C_{ortho}), 132.7 (d, J_{CP} = 136, C_{ipso}), 132.9 (d, J_{CP} = 2, C_{para}). δ_P (145.8 MHz, $CDCl_3$): +45.1. ν_{max} (KBr disk)/cm^{-1}: 1170 (s, P═O). HRMS (EI): 501.2007 (M + Na^+). Calcd for $C_{25}H_{35}NaO_7P$: 501.2018.

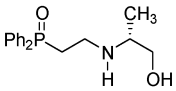
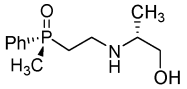
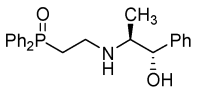
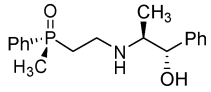
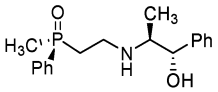
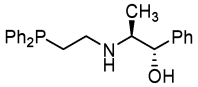
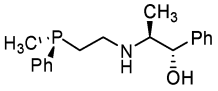
Diastereomeric Mixture (S_P/R_P)-dicyclohexylidene-D-glucose-(1-naphthyl)phenyl Phosphinate Ester, 13. White solid, 80%, mp 72−75 °C. δ_H (360 MHz, $CDCl_3$): 1.28−1.80 (20H, m, CH_2), 4.02−4.28 (3H, m, H_6, H_4), 4.38−4.54 (1H, m, H_5), 4.97−5.01 (1H, m, H_3), 5.21 (1H, d, J_{HH} = 3.6, H_2), 5.27 (1H, d, J_{HH} = 3.6, H_2), 5.96 (1H, d, J_{HH} = 3.6, H_1), 6.05 (1H, d, J_{HH} = 3.6, H_1), 7.17−8.85 (12H, m, *Ar*−*H*). δ_C (90.6 MHz, $CDCl_3$): 24.6 (s, CH_2), 24.7 (s, CH_2), 24.8 (s, CH_2), 25.6 (s, CH_2), 25.8 (s, CH_2), 26.0 (s, CH_2), 26.1 (s, CH_2), 67.0 (s, C_6), 72.2 (s, C_5), 78.0 (d, J_{CP} = 7, C_3), 82.1 (d, J_{CP} = 9, C_4), 85.2 (s, C_2), 105.4 (s, C_1), 124.0−160.0 (*Ar*−*C*). δ_P (145.8 MHz, $CDCl_3$): +35.6, +35.4. HRMS (EI): 613.2304 (M + Na^+). Calcd for $C_{34}H_{39}NaO_7P$: 613.2331.

General Procedure for the Displacement of Chiral Auxiliary. Vinylmagnesium bromide (1 M solution in THF, 2 equiv) was added dropwise, via syringe, to a solution of the corresponding phosphinate ester (3 mmol) in THF (20 mL) at −78 °C. The mixture was heated gradually to −40 °C and stirred until the reaction was complete (^{31}P NMR). The reaction mixture was quenched by transfer via cannula into a solution of 1 M aqueous NH_4Cl (100 mL) at 0 °C. Following separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 25 mL), dried ($MgSO_4$), filtered, and evaporated to furnish the crude product as an oil, which was purified by flash chromatography on silica using $CHCl_3$/acetone (8:2) as the eluting system. Solid products were recrystallized from diethyl ether.

(+)-(R_P)-Methylphenylvinylphosphine Oxide, (R_P)-14. White solid, 80%, mp 79−81 °C. $[\alpha]_D^{20}$ +81.7° (*c* 2.0, $CHCl_3$). δ_H (360 MHz, $CDCl_3$): 1.77 (3H, d, J_{HP} = 13.2, PCH_3), 6.15 (1H, ddd, J_{HP} = 40.6, J_{HH} = 12.4, 1.8, CH_2), 6.22 (1H, ddd, J_{HP} = 22.1, J_{HH} = 18.6, 1.8, CH_2), 6.42 (1H, ddd, J_{HP} = 25.1, J_{HH} = 18.6, 12.4, PCH), 7.44−7.54 (3H, m, H_{meta}, H_{para}), 7.67−7.74 (2H, m, H_{ortho}). δ_C (90.6 MHz, $CDCl_3$): 16.30 (d, J_{CP} = 74, PCH_3), 128.6 (d, J_{CP} = 12, C_{meta}), 130.6 (d, J_{CP} = 10, C_{ortho}), 131.7 (d, J_{CP} = 3, C_{para}), 132.5 (d, J_{CP} = 95, CH_2), 132.9 (s, CH), 133.2 (d, J_{CP} = 102, C_{ipso}). δ_P (145.8 MHz, $CDCl_3$): +27.7. ν_{max} (KBr disk)/cm^{-1}: 1165 (P═O). Anal. Calcd for $C_9H_{11}OP$: C, 65.06; H, 6.67. Found C, 65.27; H, 6.68%. Colorless crystals for X-ray crystallography obtained by recrystallization from diethyl ether at −5 °C.

(−)-(S_P)-Methylphenylvinylphosphine Oxide, (S_P)-14.[17] White solid, 78%, mp 79−81 °C (lit. 80 °C). $[\alpha]^{20}_D$ −81.3° (*c* 2.0, $CHCl_3$).

TABLE 5. Asymmetric Transfer Hydrogenation of Arylphenyl Ketones[a]

Entry	R	Ligand	t (h)	Conv. (%)	ee (%)	Conf.
1	Me		1	80	33	*S*
2	Et			73	31	*S*
3	*i*-Pr	(R_C)-**30**		63	6	*R*
4	Me		1	84	37	*S*
5	Et			79	35	*S*
6	*i*-Pr	(R_P, R_C)-**23**		50	11	*R*
7	Me		1	87	91	*R*
8	Et			93	90	*R*
9	*i*-Pr	(R_C, S_C)-**28**		73	90	*S*
10	Me		1	96	90	*R*
11	Et			96	88	*R*
12	*i*-Pr	(R_P, R_C, S_C)-**20**		83	85	*S*
13	Me		1	96	96	*R*
14	Et			95	94	*R*
15	*i*-Pr	(S_P, R_C, S_C)-**20**		81	90	*S*
16	Me		2	83	80	*R*
17	Et			84	75	*R*
18	*i*-Pr	(R_C, S_C)-**29**		70	69	*S*
19	Me		2	78	77	*R*
20	Et			74	73	*R*
21	*i*-Pr	(R_P, R_C, S_C)-**27**		63	69	*S*

[a] General reaction conditions: 2 mmol of the appropriate substrate in 2-propanol (20 mL), $[Ru(cymene)Cl_2]_2$ (0.01 mmol), appropriate ligand (0.04 mmol), base (0.1 mmol), 29 °C. Conversion and enantioselectivity were determined by GC analysis.

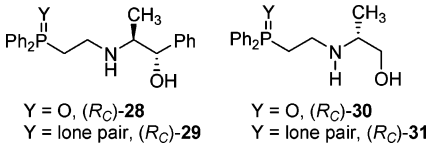


FIGURE 3. Non-P-chiral aminohydroxyphosphines included in the catalytic study.

δ_H (360 MHz, $CDCl_3$): 1.77 (3H, d, J_{HP} = 13.2, PCH_3), 6.15 (1H, ddd, J_{HP} = 40.6, J_{HH} = 12.4, 1.8, CH_2), 6.22 (1H, ddd, J_{HP} = 22.1, J_{HH} = 18.6, 1.8, CH_2), 6.42 (1H, ddd, J_{HP} = 25.1, J_{HH} = 18.6, 12.4, PCH), 7.44−7.54 (3H, m, H_{meta}, H_{para}), 7.67−7.74 (2H, m, H_{ortho}). δ_C (90.6 MHz, $CDCl_3$): 16.30 (d, J_{CP} = 74, PCH_3), 128.6 (d, J_{CP} = 12, C_{meta}), 130.6 (d, J_{CP} = 10, C_{ortho}), 131.7 (d, J_{CP} = 3, C_{para}), 132.5 (d, J_{CP} = 95, CH_2), 132.9 (s, CH), 133.2 (d, J_{CP} = 102, C_{ipso}). δ_P (145.8 MHz, $CDCl_3$): +27.7. ν_{max} (KBr disk)/cm^{-1}: 1165 (P═O).

Synthesis of β-Aminophosphine Oxides. Method A: To a solution of the appropriate vinylphosphine oxide (2.5 mmol) in 3 mL of MeOH was added the appropriate amine (3 equiv). The reaction mixture was heated in a sealed Young's tube at 80 °C. When the reaction was complete, the volatiles were removed under reduced pressure. The remaining crude product was purified by flash chromatography on silica using $CHCl_3$/acetone/Et_3N (8:2:0.5).

Method B: To a solution of the appropriate vinylphosphine oxide (3 mmol) in 3 mL of MeOH was added the appropriate amine (0.8 equiv). The reaction mixture was heated in a sealed Young's tube at 80 °C. After the appropriate reaction time, MeOH was removed and the crude product was dissolved in ether (50 mL) and subjected to an acidic work up with 1 M aqueous HCl. From the organic phase, the unreacted vinylphosphine oxide was recovered and purified via chromatography ($CHCl_3$/acetone 8:2). The aqueous phase was treated with 1 M aqueous NaOH followed by extraction with $CHCl_3$. The solvent was then removed, and the crude product was purified by flash chromatography using $CHCl_3$/acetone/Et_3N (8:2:0.5).

{2-[(R_P)-Methylphenylphosphinoyl]ethyl}-(1*R*)-(1-phenylethyl) Amine, (R_P,R_C)-17. Low-melting solid, 97%. $[\alpha]^{20}_D$ −25.5° (*c* 2.7, $CHCl_3$). δ_H (360 MHz, $CDCl_3$): 1.23 (3H, d, J_{HH} = 6.8, CHCH_3), 1.62 (3H, d, J_{HP} = 13.2, PCH_3), 1.78 (1H, br s, *NH*), 1.95−2.13 (2H, m, PCH_2), 2.56−2.84 (2H, m, CH_2N), 3.61 (1H,

q, J_{HH} = 6.8, *CH*CH_3), 7.08−7.23 (5H, m, *Ph*), 7.33−7.46 (3H, m, H_{meta}, H_{para}), 7.54−7.66 (2H, m, H_{ortho}). δ_C (90.6 MHz, $CDCl_3$): 16.4 (d, J_{CP} = 70, P*C*H_3), 24.1 (s, CH*C*H_3), 32.2 (d, J_{CP} = 70, P*C*H_2), 40.9 (d, J_{CP} = 2, *C*H_2N), 58.1 (s, *CH*CH_3), 126.4 (s, *Ph*), 126.9 (s, *Ph*), 128.3 (s, *Ph*), 128.6 (d, J_{CP} = 11, C_{meta}), 129.8 (d, J_{CP} = 9, C_{ortho}), 131.5 (d, J_{CP} = 2, C_{para}), 133.7 (d, J_{CP} = 95, C_{ipso}), 145.1 (s, *Ph*). δ_P (145.8 MHz, $CDCl_3$): +37.9. ν_{max} (thin film)/cm^{-1}: 3243 (s, NH), 1115 (s, P═O). HRMS (EI): 310.1322 (M + Na^+). Calcd for $C_{17}H_{22}NNaOP$: 310.1337.

{2-[(R_P)-Methylphenylphosphinoyl]ethyl}-(1*S*)-(1-phenylethyl) Amine, (R_P,S_C)-17. Low-melting solid, 98%. $[\alpha]^{20}_D$ +50.7° (*c* 2.8, $CHCl_3$). δ_H (360 MHz, $CDCl_3$): 1.21 (3H, d, J_{HH} = 6.8, CH*C*H_3), 1.61 (3H, d, J_{HP} = 13.2, P*C*H_3), 1.69 (1H, br, *NH*), 1.92−2.15 (2H, m, P*C*H_2), 2.60−2.74 (2H, m, *C*H_2N), 3.61 (1H, q, J_{HH} = 6.8, *CH*CH_3), 7.08−7.23 (5H, m, *Ph*), 7.33−7.46 (3H, m, H_{meta}, H_{para}), 7.55−7.64 (2H, m, H_{ortho}). δ_C (90.6 MHz, $CDCl_3$): 16.5 (d, J_{CP} = 70, P*C*H_3), 24.1 (s, CH*C*H_3), 32.1 (d, J_{CP} = 70, P*C*H_2), 40.7 (d, J_{CP} = 3, *C*H_2N), 58.0 (s, *CH*CH_3), 126.3 (s, *Ph*), 126.7 (s, *Ph*), 128.5 (s, *Ph*), 128.6 (d, J_{CP} = 11, C_{meta}), 129.8 (d, J_{CP} = 10, C_{ortho}), 131.5 (d, J_{CP} = 3, C_{para}), 133.4 (d, J_{CP} = 96, C_{ipso}), 145.0 (s, *Ph*). δ_P (145.8 MHz, $CDCl_3$): +37.8. ν_{max} (thin film)/cm^{-1}: 3243 (s, NH), 1115 (s, P═O). HRMS (EI): exact mass calcd for $C_{17}H_{22}NNaOP$ (M^+ + Na), 310.1337; found, 310.1332.

General Procedure for the Reduction of Phosphine Oxide. The appropriate aminophosphine oxide (2 mmol) was suspended in toluene (25 mL). Et_3N (6 mL) was added, and the mixture was stirred and cooled to 0 °C. Trichlorosilane (5 equiv) was added dropwise by syringe, followed by gradual warming to reflux (3−4 h). After cooling to ambient temperature, the mixture was diluted with ether (50 mL), and a few drops of aqueous Na_2CO_3 were added to destroy the excess reducing agent. The mixture was filtered through a short pad of Celite under Ar and dried over $MgSO_4$, before evaporating to dryness under reduced pressure, to give the product.

{2-[(R_P)-Methylphenylphosphanyl]ethyl}-(1*R*)-(1-phenylethyl) Amine, (R_P,R_C)-25. Colorless oil, 81%. $[\alpha]^{20}_D$ +4.7° (*c* 2.3, $CHCl_3$). δ_H (360 MHz, $CDCl_3$): 1.19 (3H, d, J_{HP} = 3.2, P*C*H_3), 1.25 (3H, d, J_{HH} = 6.8, CH*C*H_3), 1.45 (1H, br s, *NH*), 1.68−1.90 (2H, m, P*C*H_2), 2.43−2.61 (2H, m, *C*H_2N), 3.68 (1H, q, J_{HH} = 6.8, *CH*CH_3), 7.11−7.46 (10H, m, *Ar*−*H*). δ_C (90.6 MHz, $CDCl_3$): 10.7 (d, J_{CP} = 13, P*C*H_3), 23.2 (s, CH*C*H_3), 30.5 (d, J_{CP} = 12, P*C*H_2), 43.2 (d, J_{CP} = 19, *C*H_2N), 57.1 (s, *CH*CH_3), 125.5 (s, *Ph*), 125.8 (s, *Ph*), 127.2 (s, *Ph*), 127.4 (s, C_{para}), 127.6 (d, J_{CP} = 9, C_{meta}), 131.7 (d, J_{CP} = 19, C_{ortho}), 137.5 (d, J_{CP} = 12, C_{ipso}), 144.9 (s, *Ph*). δ_P (145.8 MHz, $CDCl_3$): −38.8. ν_{max} (thin film)/cm^{-1}: 3420 (s, NH). HRMS (EI): 294.1394 (M + Na^+). Calcd for $C_{17}H_{22}NNaP$: 294.1388.

{2-[(R_P)-Methylphenylphosphanyl]ethyl}-(1*S*)-(1-phenylethyl) Amine, (R_P,S_C)-25. Colorless oil, 78%. $[\alpha]^{20}_D$ +22.3° (*c* 2.5, $CHCl_3$). δ_H (360 MHz, $CDCl_3$): 1.22 (3H, d, J_{HP} = 3.2, P*C*H_3), 1.25 (3H, d, J_{HH} = 6.8, CH*C*H_3), 1.45 (1H, br, *NH*), 1.66−1.88 (2H, m, P*C*H_2), 2.43−2.61 (2H, m, *C*H_2N), 3.68 (1H, q, J_{HH} = 6.8, *CH*CH_3), 7.11−7.46 (10H, m, *Ar*−*H*). δ_C (90.6 MHz, $CDCl_3$): 10.7 (d, J_{CP} = 13, P*C*H_3), 23.2 (s, CH*C*H_3), 30.5 (d, J_{CP} = 12, P*C*H_2), 43.2 (d, J_{CP} = 19, *C*H_2N), 57.1 (s, *CH*CH_3), 125.5 (s, *Ph*), 125.8 (s, *Ph*), 127.2 (s, *Ph*), 127.4 (s, C_{para}), 127.6 (d, J_{CP} = 9, C_{meta}), 131.7 (d, J_{CP} = 19, C_{ortho}), 137.5 (d, J_{CP} = 12, C_{ipso}), 144.9 (s, *Ph*). δ_P (145.8 MHz, $CDCl_3$): −38.8. ν_{max} (thin film)/cm^{-1}: 3420 (s, NH). HRMS (EI): 294.1304 (M + Na^+). Calcd for $C_{17}H_{22}NNaP$: 294.1388.

Reduction of Aryl Ketones. A solution of $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol, 1 mol %) and the appropriate ligand (0.04 mmol, 2 mol %) in *i*-PrOH (5 mL) was placed in a dry reaction tube under argon and heated at 80 °C for 20 min, whereupon the color changed from orange to deep red. The catalyst solution was cooled to 29 °C, before the introduction of the substrate (2 mmol) as a solution in *i*-PrOH (4 mL). The reaction was initiated by the addition of a solution of KOH (0.1 mmol) in *i*-PrOH (1 mL). Reaction aliquots (0.1 mL) were extracted periodically and passed through silica, before GLC analysis. The conversions and ee's were determined using a capillary column (25 m × 0.25 mm), under isothermal conditions. Retention times: acetophenone 8.9 min, (*R*)-1-phenylethanol 14.1 min, (*S*)-1-phenylethanol 17.9 min at 100 °C; propiophenone 15.1 min, (*R*)-phenylpropanol 42.1 min, (*S*)-phenylpropanol 47.7 min at 100 °C; 2-methylpropiophenone 10.5 min, (*R*)-2-methyl-1-phenylpropanol 34.6 min, (*S*)-2-methyl-1-phenylpropanol 36.8 min at 110 °C. Absolute configurations were determined by comparing the optical rotation with reported vales.

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Supporting Information Available: Experimental procedures and characterization data for precursors **1**−**6**, compounds **9**−**12**, **13**, **15**, **16**, **18**−**24**, **26**, and **27**, selected NMR spectra of intermediates, X-ray crystallographic data, and cif files for compounds **14** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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